Chapter 5
Biventricular Pacing for Patients with Complete Heart Block

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Introduction and Etiologies of CHB

Complete heart block (CHB), or third-degree atrioventricular block (AVB), is defined by a failure of supraventricular impulses to conduct through the AV node or His bundle. The diagnosis requires that atrial impulses occur at a higher rate than the ventricular rate and that no atrial stimuli lead to ventricular contractions [1]. According to ACC/AHA/HRS guidelines, pacemaker implantation is a class I indication in all patients with advanced second-degree or third-degree AVB who have symptomatic bradycardia, any degree of LV dysfunction, an escape rhythm <40 beats per minute, asystolic pauses >3.0 seconds, or any escape rhythm generated from below the AV node as a means to reduce mortality secondary to sudden cardiac death [2, 3]. The guidelines also specify that it is reasonable (class IIa) to consider permanent pacemaker implantation for persistent third-degree AV block with an escape rate greater than 40 bpm in asymptomatic adult patients without cardiomegaly.

The etiologies of complete heart block are numerous and can be grouped into congenital and acquired AVB (with the latter being significantly more common). Congenital complete atrioventricular block (CCAVB) is a rare entity; it occurs in approximately 1 out of every 15,000–20,000 live births and is mechanistically thought to be due to in utero exposure to maternal antibodies (anti-Ro/SSA and

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anti-La/SSB antibodies) leading to inflammatory changes and fibrosis of the conduction system in most cases, although inherited channelopathies may also play a role [4]. It is primarily associated with a junctional escape rhythm and may be associated with a benign clinical course and late diagnosis. Overall mortality, however, in CCAVB without intervention is estimated to be as high as 16% in the neonatal period [5]. Other congenital heart diseases such as hypoplastic left heart syndrome, right and left isomerism, univentricular heart, and L-shaped ventricle are also associated with spontaneous high-degree AVB including complete AVB. The proposed mechanisms include poor coronary supply to both sinoatrial (SA) and atrioventricular (AV) nodes in altered cardiac anatomy with subsequent ischemic damage during the third trimester [6]. Development of a superficial, and perhaps unstable, conduction system is also observed in CHD. CHB may occur due to structural defects within the myocardium such as in AV septal defects or iatrogenically after corrective cardiac surgery.

Acquired complete heart block can occur at any age and can be due to a multitude of causes including iatrogenic, infectious, ischemic, and malignant (see Table 5.1). CHB is a well-accepted indication for permanent pacemaker placement, in both pediatric and adult patients, as well as for the asymptomatic patient who exhibits other signs of high-risk for malignant arrhythmia and sudden cardiac death. This review will discuss the current evidence supporting the use of cardiac resynchronization therapy (CRT) versus conventional right ventricular pacing (RVP) in the setting of CHB.

Table 5.1 Causes of complete heart block

Infectious	Lyme myocarditis Chagas myocarditis Diphtheric myocarditis Rheumatic fever
Inflammatory	Sjogren's syndrome Cardiac sarcoidosis
Ischemic	Myocardial infarction Aortic dissection
Structural	Post-cardiac surgery Post-transcatheter aortic valve insertion/replacement
Malignant	Primary cardiac lymphoma or metastasis Head and neck cancers with loss of baroreceptor and/or neurocardiogenic response
Medications	Beta blockers Non-dihydropyridine calcium-channel blockers (e.g., verapamil, diltiazem) Digoxin Clonidine Findolamid (used to treat multiple sclerosis) Adverse effect of checkpoint inhibitors
Metabolic	Hyperkalemia Hypermagnesemia Hypothyroidism

Indications for CRT

The 2013 update of ACCF/AHA/HRS practice guidelines for device-based therapy established clear indications for CRT therapy in patients with reduced LVEF, primarily 35%, and symptomatic heart failure (see Table 5.2) [3]. These guidelines were founded on the results of large multicenter randomized controlled trials showing echocardiographic, functional, and mortality benefit when comparing CRT-D to ICD and intrinsic conduction on guideline-directed medical therapy [7–12]; however, these trials did not specifically enroll patients with CHB.

Table 5.2 Indications for cardiac resynchronization therapy (CRT)

Class I	CRT is indicated for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA class II, III, or ambulatory IV; symptoms on GDMT *(Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II)*
Class IIa	CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120–149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT (*Level of Evidence: B*)
	CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT (*Level of Evidence: A*)
	CRT can be useful in patients with atrial fibrillation and LVEF less than or equal to 35% on GDMT if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT (*Level of Evidence: B*)
	CRT can be useful for patients on GDMT who have LVEF less than or equal to 35% and are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing (*Level of Evidence: C*)
	In patients with atrioventricular block who have an indication for permanent pacing with an LVEF between 36% and 50% and are expected to require ventricular pacing more than 40% of the time, it is reasonable to choose pacing methods that maintain physiologic ventricular activation (e.g., cardiac resynchronization therapy [CRT] or His bundle pacing) over right ventricular pacing (*Level of Evidence: B-R) (new)*
Class IIb	CRT may be considered for patients who have LVEF less than or equal to 30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration of greater than or equal to 150 ms, and NYHA class I symptoms on GDMT (*Level of Evidence: C*)
	CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120–149 ms, and NYHA class III/ambulatory class IV on GDMT (*Level of Evidence: B*)
	CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class II symptoms on GDMT (*Level of Evidence: B*)
Class III	CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration less than 150 ms (*Level of Evidence: B*)
	CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year (*Level of Evidence: C*)

Outside the realm of sinus rhythm, the 2013 practice guidelines make a class IIa recommendation for CRT in patients with atrial fibrillation and LVEF ≤35% on guideline-directed medical therapy who otherwise meet criteria for CRT implantation as well as for those with atrial fibrillation who have received AV nodal ablation or pharmacologic rate control requiring near 100% ventricular pacing [3]. The recently released 2018 ACC/AHA/HRS guidelines on the evaluation and management of patients with bradycardia and cardiac conduction delay also provide a class IIa recommendation for consideration for CRT or His bundle pacing in patients with LVEF between 36% and 50% who are anticipated to receive >40% ventricular pacing [2].

CRT in Heart Failure with Reduced Ejection Fraction (LVEF ≤35%)

While multiple studies have been performed in CRT in patients with heart failure, there have only been two randomized controlled trials (RCTs) conducted to date comparing RVP with CRT in the setting of reduced LVEF. The 2006 Homburg Biventricular Pacing Evaluation (HOBIPACE) trial was the first trial to address RVP versus CRT in patients with a standard antibradycardia indication [13]. The study was a single-center, single-blind, prospective RCT of 30 patients with LVEF <40% and LV end-diastolic diameter ≥60 mm with NYHA class III–IV symptoms on optimal medical management. The enrolled population had an average LVEF of 26% and an average QRS duration of 174 ms. All patients received atrio-biventricular devices and were randomized to either RVP or CRT and received 3 months of therapy prior to crossing over to the other pacing mode. Primary endpoints measured were LVEF, left ventricular end-systolic volume (LVESV), and peak oxygen consumption. Secondary endpoints measured were NYHA functional class, quality of life as assessed by questionnaire, and serum concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

When compared with RVP, patients receiving CRT showed significantly reduced LVESV (17% decline), significantly increased LVEF (22% rise), and significantly increased peak oxygen consumption (12% increase) during biventricular stimulation. Secondary endpoints of left ventricular end diastolic volume (LVEDV) and NT-proBNP were also significantly reduced in the CRT compared with RVP. They also found other measures of favorable LV remodeling, including significant decrease in LV mass and subsequent increase in hypertrophy index in CRT as compared to RVP. No difference in mortality was found, although the study was underpowered for this endpoint.

Patients with atrial fibrillation and AVB were included in HOBIPACE. Over one-third (11 or 37%) of patients demonstrated AF at enrollment, with 9 patients who continued to be in permanent atrial fibrillation throughout the course of the study. Subgroup analysis of AF patients did not show any difference in echocardiographic or clinical outcomes compared to those in sinus rhythm. Taken together, the results of HOBIPACE provided compelling support of CRT over traditional RVP in those with reduced LVEF and prolonged QRS duration; however, this study did not evaluate patients with high-degree AVB [13].

The only other RCT evaluating CRT versus RVP in patients with reduced LVEF is the 2010 Conventional Versus Biventricular Pacing in Heart Failure and Bradyarrhythmia (COMBAT) trial [14]. This study was a multicenter, prospective, double-blind crossover study of 60 patients. Patients enrolled had an average LVEF of 29–30%, QRS duration of 148–154 ms, and NYHA class II–IV symptoms. Fifty percent of all patients had CHB in this study. Patients underwent a minimum of 3-month intervals of RVP/CRT/RVP pacing or CRT/RVP/CRT pacing modalities and were ultimately followed for 17.5 months. Primary endpoints evaluated were quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire and NYHA functional class. Secondary endpoints were 6-min walk test, peak oxygen consumption during cardiopulmonary exercise, echocardiographic parameters, and mortality.

Patients receiving biventricular stimulation in COMBAT showed significant improvement in all primary endpoints at the end of each crossover period, as well as LVEF and LVESV. There was no significant difference between modalities in 6-min walk test or peak oxygen consumption. Of the 25% of patients who died during the study period, they were significantly more likely to be in a RVP period than during CRT period. COMBAT did not include patients in atrial fibrillation (in contrast to HOBIPACE), had stricter LV lead placement requirements, and was double-blind compared to single-blind design. Although also small in comparison the landmark trials that led to the approval of CRT for primary prevention indications, COMBAT showed supportive data, particularly with respect to echocardiographic and clinical parameters—that a biventricular pacing mode was superior to RVP in patients with high-degree AVB and reduced LVEF (see Table 5.3).

More recently, a nonrandomized study examining the role of CRT in patients with heart block and low LVEF was conducted by Shimano and colleagues in 2007 [15]. They sought to evaluate the treatment of patients with RV pacing-induced cardiomyopathy and evaluated 18 patients with acquired CHB who had received RVP and subsequently developed pacemaker-induced cardiomyopathy and heart failure. The average LVEF at the time of upgrade was 28%, whereas the original LVEF at the time of device placement was 54%. Patients had received a mean of 81 months of RVP prior to upgrade. This study followed patients for 12 months after device upgrade from RVP to CRT-D or LV-ICD devices. The results of this study showed significantly improved LVEF (28% to 34%), NYHA functional class (mean 3.0–1.9), as well as reduced LV end-diastolic diameter, left atrial diameter, mitral regurgitation severity, and serum BNP level. Heart failure hospitalization rate per year was also significantly reduced after upgrade to CRT from 2.1 per year to 0.3 per year [15].

CRT in Patients with Preserved Ejection Fraction (LVEF ≥50%)

To date, there have been three RCTs that have evaluated the role of CRT compared with RVP in patients with preserved LVEF. The first was the Pacing to Avoid Cardiac Enlargement (PACE) trial in 2009 [16]. A multicenter, prospective, double-blind

Table 5.3 Randomized controlled trials evaluating cardiac resynchronization therapy in patients with high-degree AV block and heart failure with reduced ejection fraction (≤35%)

Clinical trial or study	Study design	Population	QRS duration (mean)	LVEF (mean)	Summary of findings
HOBIPACE (2006)	Single-center, prospective, single-blinded RCT Crossover comparison of RV and BiV pacing of patients with symptomatic bradycardia requiring permanent pacemaker Followed for 6 months: 3 months of each pacing modality	*N* = 30 patients Mean age 69.7 years old NYHA class III–IV, LVEF <40%, and LVEDD ≥60 mm Included atrial fibrillation patients (11/30 patients)	174 ms	26%	Significantly lower LVEDV, LVESV, and NT-proBNP in BiV group Significantly higher LVEF, cardiac index, and peak O2 consumption in BiV group Improved exercise capacity and quality of life in BiV group
COMBAT (2010)	Multicenter, prospective, double-blind RCT Crossover study of RVP versus BiV pacing in those with AV block as an indication for pacing Followed for average of 17.5 months, minimum of 3 months in each pacing modality	*N* = 60 patients: 31 patients underwent RVP/BiV/RVP, 29 patients underwent BiV/RVP/BiV Mean ages 57.4/59.3 years old NYHA class II–IV, LVEF ≤40%, and on optimal medical therapy for 30 days Excluded atrial fibrillation patients	148 ms (RVP) 154 ms (BiV) 15/31 and 15/29 patients in each arm had complete heart block	29% (RVP) and 30% (BiV)	Significant improvement in quality of life, NYHA class, LVEF, and LVESV with BiV pacing 15/60 (25%) patients died. Of these, significantly more were in an RVP period

trial, PACE enrolled 177 patients with symptomatic bradycardia and preserved LVEF ≥45% (average LVEF 62%) and randomized patients to conventional RV apical pacing or CRT. The original study followed patients for 12 months [16], and a 24-month follow-up was subsequently published in 2011 [17]. The average QRS duration was 107 ms, and approximately 50–60% of patients had advanced AVB as indication for pacemaker placement. Primary endpoints evaluated were LVEF and LVESV.

After 24 months, LVEF significantly decreased in the RVP group (62–53%), and this was also a significant difference when compared to patients receiving biventricular pacing, who demonstrated preservation of LVEF over the study period (62–63%). Similarly, LVESV significantly increased in RVP (28.4–38.3 mL over

24 months) and also was significantly increased compared to CRT (28.2–25.3 mL over 24 months). However, there were no significant differences in clinical measures such as heart failure hospitalizations, mortality, or quality of life between groups [16, 17]. Although the results of PACE argue in favor of biventricular pacing to protect LVEF and structural parameters, this did not translate to clinical outcomes during the studied period in patients with preserved LVEF and a narrow QRS complex at baseline.

Shortly after PACE, the authors of the Preventing Ventricular Dysfunction in Pacemaker Patients Without Advanced Heart Failure (PREVENT-HF) trial reported similar findings 2 years later. PREVENT-HF was an international multicenter, prospective, single-blind study of 108 patients with normal LVEF undergoing device implant for AV block which randomized patients to receive either DDD-R dual-chamber RV apical pacing or biventricular pacing systems. This trial selected patients with class I or IIa indication for permanent pacemaker and with an anticipated overall pacing rate of ≥80%. The groups were well-matched, with no significant differences in LVEF (55% RVP versus 58% CRT), QRS duration (121 ms RVP versus 124 ms CRT), and other basic demographics including gender and major comorbidities. Patients were randomized to RV apical pacing or biventricular pacing strategies and followed for 12 months. Of note, however, there was significant crossover due to inability to implant an LV lead affecting 16% of the patients assigned to biventricular pacing. The primary endpoint measured was change in LVEDV, and secondary endpoints evaluated were LVESV, LVEF, mitral regurgitation, and clinical composite of heart failure events or cardiovascular hospitalization. This trial showed no significant difference in any of the outcomes measured in patients with high degree of ventricular pacing and preserved LVEF, although the authors noted that follow-up time was short and that small numeric improvement in LVEF (but not reaching statistical significance) was noted in patients receiving biventricular pacing in the on-treatment analysis [18].

Most recently, the Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BioPace) study was performed and preliminary data released in 2014, although the final manuscript remains unpublished. BioPace was a large, multicenter, prospective, single-blind RCT enrolling 1,810 patients, and its findings with respect to the impact of biventricular pacing has been highly anticipated. Enrollment criteria were broad, including patients NYHA class I–III symptoms irrespective of LVEF. The most important requirement was AV block and anticipated need for ventricular pacing ≥67% of the time. BioPace included patients with atrial tachyarrhythmias (24% of patients). Of these patients, 400 (22%) had CHB, and an additional 573 (32%) had intermittent CHB or type II second-degree AVB. Patients were then randomized to RV versus biventricular pacing systems and followed for an average of 5.6 years. Baseline QRS duration overall was 119 ms. LVEF overall in all patients was 55%; if further broken down, 1239/1810 (68%) of patients had LVEF >50%; of these, the average LVEF was 62% [19].

The primary endpoint assessed in BioPace was a combined clinical endpoint of time to death and time to first heart failure hospitalization. The preliminary analysis

showed no significant difference in the primary outcome between RVP and biventricular pacing strategies; this remained true even substratifying based on LVEF >50% and LVEF ≤50% subgroups [20]. Since the final manuscript has not been published, we do not have data regarding if there were subgroups of benefit with CRT, such as those with higher-degree RV pacing or high-degree AV block. At this point, however, the results are not suggestive of uniform benefit of CRT in patients with normal LVEF.

Taken together, three RCTs, BioPace, PREVENT-HF, and PACE, all resulted in no difference in hard clinical outcomes for patients who received CRT versus RVP with preserved LVEF (see Table 5.4) as a de novo strategy. This is an interesting contrast with studies like Shimano's which show that—for patients with normal LVEF at baseline who develop RV pacing-induced cardiomyopathy after months or years of pacing—biventricular upgrade is a reasonable treatment approach. These findings suggest that the population of patients with normal LVEF at baseline and anticipated need for high-degree of RV pacing is heterogenous and that we must investigate other possible indicators or signals of risk prior to upfront biventricular pacing.

More recent registry data from Merchant et al. investigated 21,202 patients, of whom close to one-third had a documented history of complete heart block [21]. They found that patients with preexisting complete heart block were more likely to demonstrate a new diagnosis of heart failure in follow-up than patients without this diagnosis (and therefore likely receiving less RV pacing). With respect to predictors of heart failure, they found that younger age (≤55 years old) and history of atrial fibrillation were significant predictors of both increased heart failure early (within 6 months) and late (between 6 months and 4 years) after device implant. An important limitation of this study, however, is that baseline LVEF and pacing burden were not retrievable, and therefore interpretation with respect to patient selection remains limited from these large registry data.

CRT in Patients with Intermediate Ejection Fraction (LVEF 36–49%)

In patients with intermediate LVEF, there have been two RCTs that have evaluated the role of RVP versus biventricular pacing. The first of these is the Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation (PAVE) study, which was published in 2005 [22]. PAVE was a multicenter, prospective, single-blind RCT of 184 patients who were to receive AV nodal ablation for chronic atrial fibrillation with rapid ventricular response refractory to medical management. This post-AV nodal ablation population was targeted given the need for post-ablation pacemaker placement and the inference that patients would be primarily reliant on ventricular pacing for nearly 100% of ventricular beats. Patients with NYHA class II–III symptoms and no previous pacemaker or implantable cardioverter-defibrillator

Table 5.4 Randomized controlled trials evaluating cardiac resynchronization in patients with high degree AV block and preserved ejection fraction (EF ≥50%)

Clinical trial or study	Study design	Population	QRS duration (mean)	LVEF (mean)	Summary of findings
PACE (2009)	Multicenter, prospective, double-blind RCT of patients with indication for primary pacemaker and preserved ejection fraction BiV or RVP pacing Followed for 12 months in original study Follow up study performed at 24 months	*N* = 177 89 patients in BiV pacing group, 88 patients in RVP group Mean age 68–69 years old Indication for PPM: SND, high-degree AVB LVEF≥45% Excluded if in persistent AF, unstable angina, ACS, or PCI/CABG within previous 3 months Included patients with permanent AF	107 ms 55/88 had advanced AVB in RVP group 49/89 had advanced AVB in CRT group	62%	Significantly lower LVEF and higher LVESV in RVP group LVEF and LVESV unchanged in BiV pacing group No difference in death, HF hospitalization, or QOL assessment
PREVENT-HF (2011)	Multicenter, prospective, single-blind RCT of patients with normal LVEF and class I or IIa indication for PPM with need for ventricular pacing ≥80% of the time Followed for 12 months	*N* = 108 58 patients in RVP and 50 patients in CRT Mean age 70–72 years old Excluded NYHA class III–IV, MI, or cardiac surgery in previous 3 months, hypertrophic cardiomyopathy, or previous device	121 ms in RVP group 124 ms in CRT group 13/58 patients in RVP and 10/50 patients in CRT were dependent on PPM inferring high-degree AVB	55% in RVP group 58% in CRT group	Followed for 12 months: no significant difference in LVEDV, LVEF, LVESV, development or worsening MR, heart failure symptoms, cardiac mortality, or hospitalization
BioPace (2014)	Multicenter, prospective, single-blind RCT of 1810 patients with high-degree AV block requiring >67% ventricular pacing and NYHA class I–III symptoms comparing RVP versus BiV pacing Mean follow up 5.6 years	*N* = 1810 902 patients in BiV, 908 patients in RVP Mean age 74 years old LBBB present in 17% of patients overall, 24% with atrial tachyarrhythmia	119 ms overall 400/1810 patients were indicated for complete heart block 573/1810 patients were indicated for intermittent third-degree AV block or type II second-degree heart block with prolonged PR interval	55% overall 1239/1810 patients with LVEF >50%. Of these, mean EF 61.9%	No significant difference in combined endpoint of time to death and time to first heart failure hospitalization, which remained nonsignificant despite subgroup analysis by LVEF ≤50% and LVEF >50%

(ICD) were included. Baseline LVEF was 46%. Patients were then randomized to receive either a conventional RVP device or a biventricular device and subsequently underwent AV nodal ablation within the following 4 weeks. Notably, 146 patients were originally randomized to the CRT group; however, 23 patients were lost to follow-up and 21 patients were withdrawn due to failed LV lead placement. Comparatively, 106 patients were randomized to the RVP group, of which 25 were lost to follow-up, but all device implantation procedures were completed successfully. This again highlights the technical difficulty of biventricular placement over traditional dual-chamber devices [22]. Patients were followed for 6 months' duration.

The primary endpoint studied in PAVE was 6-min walk test distance before and after the study period. Secondary endpoints included quality of life as assessed by SF-36 Health Status Scale survey and LVEF. Compared to RVP, patients who received CRT had significantly improved 6-min walk distance (31% improvement from baseline compared to 24% improvement in RVP group). This change was primarily driven by patients with LVEF ≤45%, and in further subgroup analysis, 6-min walk distance was not significantly different between pacing modalities in patients with LVEF >45%. Additionally, LVEF remained unchanged at 6 months in the CRT group, but LVEF significantly decreased in the RVP group (46–41%). There was no significant difference in quality of life at 6 months post-ablation, even when further broken down by NYHA functional class, nor was there a significant difference in mortality between groups. Thus, PAVE showed evidence of clinical improvement as determined by 6-min walk distance in patients with LVEF ≤45% in favor of CRT over RVP as well as relative preservation of LVEF. However, this did not translate to a significant mortality benefit (although the trial was underpowered to show this), and it is clear that the favorable outcomes for CRT patients were driven by those with clinical heart failure and lower LVEF at baseline.

Following PAVE, which was specific to post-AV nodal ablation patients with refractory atrial fibrillation, the landmark Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction (BLOCK HF) Trial was published in 2013 [23]. BLOCK HF was a multicenter, prospective, double-blind RCT of 691 patients with mild-moderate heart failure and high degree of ventricular pacing. Patients were included with third-degree AVB (with 47% enrolled with CHB), advanced second-degree AVB, or first-degree AVB with PR interval ≥300 ms when paced at 100 bpm and LVEF ≤50% with NYHA class I–III symptoms. The study also included patients with permanent atrial fibrillation and those undergoing AV nodal ablation. Importantly, 207 patients received ICD placement as well. Patients were randomized to CRT or RVP and followed for an average of 37 months [23]. BLOCK HF demonstrated significant technical difficulty with device implantation in which 113/809 patients in whom device implantation was attempted had a serious adverse effect within the first 30 days after implantation, of which 83 patients had complications related to the implantation procedure or the CRT device itself. Adverse events included lead dislodgement, lead damage, failure to capture, implantation site infection, and atrial fibrillation.

The primary endpoint studied in BLOCK-HF was time to death of any cause, an urgent care visit for heart failure requiring intravenous medical therapy, or a ≥15% increase in LVESV index. Secondary endpoints included two clinical composite outcomes: urgent care visit for heart failure or death of any cause and heart failure hospitalization or death of any cause. The primary endpoint occurred significantly more in the RVP group compared to the CRT group with a hazard ratio of 0.74, which remained consistent between those with and without ICD placement. Similarly, when LVESV index information was removed, the primary endpoint of time to death of any cause or an urgent care visit for heart failure significantly favored CRT over RVP. The composite secondary endpoints and time to first heart failure hospitalization were significantly less in the CRT group compared to RVP, although all-cause mortality was not significantly different between groups.

A subgroup of the previously discussed BioPace trial had intermediate LVEF (41%). This subgroup was comprised of 571/1810 (32%) patients [20]. When analyzed separately, this group similarly did not show a significant difference in the primary outcome of combined time to death and time to first heart failure hospitalization. The results of BioPace, BLOCK HF, and PAVE have conflicting results in regard to clinical outcomes of CRT versus RVP in patients with intermediate LVEF (Table 5.5). Where BLOCK HF and PAVE found evidence of at least some degree of clinical improvement with CRT over traditional RV apical pacing in patients with CHB or advanced AVB, BioPace, the largest RCT conducted to date on this population, did not find a significant difference, although it remains unpublished. The 2018 bradycardia guidelines, however, have incorporated the results of BLOCK-HF, and biventricular pacing (or His bundle pacing) may be considered (class IIa indication) in patients receiving device therapy with an anticipated >40% pacing and an LVEF of 36–50%.

Congenital Heart Block

CHD and CCAVB are a special patient population with a unique array of clinical features. Many infants with CCAVB or other structural cardiac abnormalities will require pacemaker placement with or without ICD placement due to symptomatic bradycardia, progressive LV dysfunction, malignant arrhythmia or as primary prevention. Although there are no randomized controlled trials comparing traditional RVP and biventricular pacing, in this population, several case reports and case series do exist in the literature (see Table 5.6) which suggest that biventricular pacing may be of benefit.

A multicenter cross-sectional study of 178 children with structurally normal hearts, advanced second-degree or third-degree AVB, and >70% ventricular pacing requirement was conducted by Janousek et al. and published in 2013. Notably, 171/178 patients had CHB, and 138/178 patients had CCAVB. Patients underwent ventricular pacemaker placement at various locations including RVOT, RV lateral wall, RV septum, RV apex, LV basal wall, LV lateral wall, and LV apex. Patients

Table 5.5 Randomized controlled trials evaluating cardiac resynchronization in patients with high-degree AV block and intermediate ejection fraction (36–49%)

Clinical trial or study	Study design	Population	QRS duration (mean)	LVEF (mean)	Summary of findings
PAVE (2005)	Multicenter, prospective, single-blind RCT of patients undergoing AVN ablation for chronic AF with RVR refractory to medical therapy with subsequent pacemaker implantation: BiV device or RVP device Followed for 6 months	*N* = 184 103 patients in BiV groups, 81 patients in RVP group Mean age 67 years old in RVP, 70 years old in BiV group NYHA class II–III symptoms Excluded NYHA class IV, required ICD, cardiac surgery, or prosthetic valve present		46%	Significantly improved 6-min walk distance in BiV group, driven by those with LVEF ≤45% No significant difference in 6-min walk distance between groups when LVEF >45% Significant drop in LVEF in RVP group, which was avoided in BiV group No significant difference in quality of life assessment
BLOCK-HF (2013)	Multicenter, prospective, double-blind RCT comparing RVP to CRT in patients with mild-moderate heart failure, LVEF≤50%, and high degree of ventricular pacing High degree of ventricular pacing defined as: third-degree AV block, advanced second-degree block, or first-degree block with PR interval ≥300 ms when paced at 100 bpm (class I or IIa indication for PPM) NYHA class I–III symptoms and LVEF ≤50% Included patients with permanent atrial arrhythmias and post-AVN ablation Followed for average of 37 months	*N* = 691 patients: 346 in CRT, 342 in RVP 13 crossed over from BiV to RVP 84 crossed over from RVP to BiV 207 received ICD, 484 did not have ICD 97.0–98.6% ventricular pacing Mean age 73 years old	123 ms (RVP) 124 ms (CRT) 47% of all patients had third-degree AV block	40%	Primary endpoint: time to an urgent care visit for HF requiring IV therapy, time to all-cause mortality, or ≥15% increase in LVESV index significantly improved in CRT group Secondary endpoints: composite outcome of heart failure hospitalization or death and time to first HF hospitalization significantly improved in CRT group over RVP in both ICD and pacemaker groups
BioPace (2014)	Multicenter, prospective, single-blind RCT of 1810 patients, design outlined previously	*N* = 1810	119 ms overall	571/1810 patients with LVEF ≤50%: of which mean EF 41%	No significant difference in combined endpoint of time to death and time to first heart failure hospitalization, which remained nonsignificant despite subgroup analysis by LVEF ≤50% and LVEF >50%

Table 5.6 Studies evaluating cardiac resynchronization therapy in congenital heart disease with high-degree AV block

Study name	Study design and population	QRS duration (mean)	LVEF (mean)	Summary of findings
Janousek et al. (2013)	Multicenter cross-sectional study of 178 children with structurally normal hearts and indication for PPM: second- or third-degree heart block with predicted >70% ventricular pacing Median age at implantation: 3.2 years old Median pacing duration 5.4 years	171/178 patients had complete heart block 138/178 patients had congenital CHB	Pre-implantation: all groups >60% Post-implantation: RVP: 53%, LVP 60%	Significant drop in LVEF and LV shortening fraction in all RV pacing and LV basal pacing sites; no significant drop in LVEF or LV shortening fraction in LV apical or LV lateral wall pacing Observable dyssynchrony by ECHO in RVOT and RV lateral wall pacing compared to other pacing sites RV septum not significantly improved compared to other RV pacing sites LV basal pacing inferior to LV apex and LV lateral wall Maternal antibodies not a predictor of LV dysfunction
Motonaga and Dubin (2014)	Systematic review of CRT in pediatric patients with HF and CHD 7 single-center and 2 multi-center retrospective studies of HF in CHD	166 ms in multicenter reviews 66/101 of patients from single-center studies with complete AVB	26–27% in multicenter reviews	All studies found an increase in LVEF and decreased QRS duration 10–30% nonresponder rate, defined as no change in NYHA or <10% improvement in LVEF, among these reviews

were followed for a median of 5.4 years. This study observed a significant decrease in LVEF in all RV pacing sites and LV basal pacing compared to LV lateral wall and LV apical pacing sites with the most subjective ventricular dyssynchrony occurring at RVOT and RV lateral wall sites [24]. Although not specifically engaged in CRT, this study supports the concept that worsening ventricular dyssynchrony by non-physiologic cardiac conduction, even in children with structurally normal hearts and preserved LVEF, is deleterious compared to synchronous ventricular contraction.

In 2014, Motonaga and Dubin conducted a systematic review of CRT in CHD and associated heart failure. This review incorporated seven single-center studies and two multicenter retrospective studies. This review specifically identified 66/101 patients to have complete AVB. Prior to implantation, baseline QRS was 166 ms in the multicenter reviews, and baseline LVEF was 26%. All studies found increased LVEF after CRT implantation and narrowed QRS complex compared to baseline [25]. Although CRT was not compared to any other form of pacing in these studies, it may provide one of several non-pharmacologic therapies for pediatric patients with CHD and heart failure with or without complete AVB.

Post-AV Nodal Ablation

In addition to the findings of the PAVE trial (2005), a large retrospective observational cohort study using the MarketScan Commercial and Medicare supplemental claims database was performed regarding patients with atrial fibrillation who underwent AV junction ablation (AVJA) followed by pacemaker implantation [26]. The study included 24,361 patients, of which 1611 underwent AVJA, 23,377 received RVP, and 984 received biventricular pacemakers. The study compared risk of hospitalization due to atrial fibrillation between AVJA and non-AVJA groups, finding a significant reduction in the AVJA group (hazard ratio 0.31). They also compared risk of heart failure hospitalization in CRT versus RVP and found a significant increase in risk in patients who received RVP after AVJA compared to non-AVJA (hazard ratio 1.63), whereas no-such increased risk occurred in those who received CRT after AVJA.

Another prospective, double-blind, multicenter, randomized controlled trial of 186 patients by Brignole and colleagues in 2011 compared patients who had undergone AVJA for symptomatic permanent atrial fibrillation who then received biventricular pacing versus traditional RVP [27]**.** Average LVEF at enrollment was 38% in the CRT group ($N = 97$) and 37% in the RVP group ($N = 89$). 40% of patients received ICD placement as well in both groups, and 50% of patients in both groups had baseline QRS $\geq$120 ms. Patients were followed for a median of 20 months with crossover due to clinical failure as defined by the primary endpoint of composite HF hospitalization, death due to HF, or clinically worsening HF. This study found a statistically significant reduction in the primary endpoint in those who received CRT over RVP primarily driven by reduction in HF hospitalization and clinically worsening HF. All-cause mortality was similar between groups.

In patients with LVEF ≤35%, QRS ≥120 ms, and NYHA class ≥III–IV, which represented 25% of study patients and the population indicated for CRT by both American and European guidelines, there was a significant clinical decline as defined by incidence of the primary outcome in RVP as compared to CRT. Interestingly, among the 75% of patients who did not meet the above criteria, the statistical significance of clinical performance remained present favoring CRT over RVP.

Discussion

It has been well-established that nonreversible CHB is usually an unstable bradyarrhythmia that requires pacemaker support. Overall, there are limited data directly comparing RVP versus biventricular pacing with an LV lead in patients receiving devices for high-degree AV block. We believe that the available data suggest that a tailored approach of selecting RV versus biventricular pacing should be pursued based on underlying LVEF, pacing burden, and clinical scenario.

In patients with CHB and reduced LVEF ≤35%, evidence from two prospective, randomized trials—HOBIPACE and COMBAT—along with data from multiple cohort studies, consistently show echocardiographic and clinical improvement in CRT over traditional RV apical pacing. Improved LVEF (see Fig. 5.1), LV dimensions, cardiac index, exercise capacity, and quality-of-life scores were observed among these trials. These findings may correlate with the degree of ventricular dyssynchrony and prolonged QRS duration documented in both studies, with average-paced QRS dura-

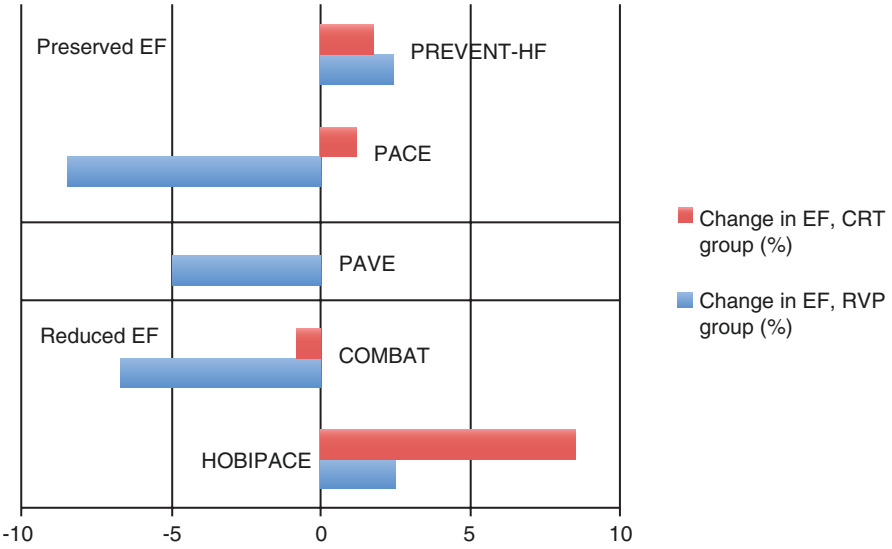

Fig. 5.1 Comparison of change in ejection fraction between RVP and CRT groups in randomized controlled studies

tions greater than 150 ms. It has also been well documented that RVP leads to an abnormal LV electrical activation sequence and functional LBBB and thus may lead to inefficient ventricular contraction and worsening LVEF over time even in patients with previously normal LVEF [28, 29]. It is thought that this abnormal electrical activation predisposes to increased mechanical work at the level of myocardial fibers with increased oxygen consumption [30–32]. The benefit of CRT in patients with reduced LVEF and prolonged QRS duration independent of AVB has also been demonstrated as well [33]. Given the consistency of data showing clinical improvement in patients with high-degree AVB and significant systolic dysfunction (≤35% at baseline), CRT is the most appropriate choice in this population.

In patients with preserved LVEF, however, the current data do not support *routine* selection of CRT over RVP. BioPace and PREVENT-HF found no significant differences in clinical or echocardiographic parameters between RVP and CRT groups. PACE found preservation of LVEF in CRT compared to RVP, but again this study showed no evidence of significant clinical change within the study time frame. More recent large registry data of patients with AVJA suggest that biventricular pacing is associated with less heart failure hospitalization, but data on remodeling or LVEF is unavailable [26]. Importantly, implantation of a left ventricular lead is a technically more advanced procedure and is associated with a higher rate of complications than traditional RVP. In 2012, the European Heart Rhythm Association/HRS expert consensus reported 5–9% implantation failure and 3–7% coronary sinus lead dislodgement [34]. Therefore, without clinical benefit and elevated procedural risk, the current data do not support the routine use of CRT over traditional RVP in patients with CHB and preserved LVEF. Nonetheless, patients should be closely followed with attending to the development of pacemaker-induced cardiomyopathy given the degree of ventricular pacing required in complete AVB. In patients who develop pacing-induced dysfunction, CRT upgrade is a reasonable approach. Not focused on this chapter, His bundle pacing (HBP) may also be another means of addressing pacing-induced cardiomyopathy and is under current study [35].

Device selection should be tailored more carefully in patients with intermediate LVEF and CHB. While BLOCK-HF (average LVEF of 40%) was a positive study and showed significant improvement in combined clinical outcomes with CRT over RVP, a subgroup of BioPace found no change in clinical outcomes between pacing modalities (although rates of pacing have yet to be reported). PAVE additionally found echocardiographic improvement with CRT and maintenance of LVEF but was driven by patients with lower LVEFs. CRT implantation can be considered in this population depending on implantation risk, comorbidities, and risk of development of pacemaker-induced cardiomyopathy. There is a growing consideration for use of HBP in this population. Randomized controlled trials are ongoing to assess efficacy and safety of HBP compared with LV and biventricular devices. A systematic review of HBP cases from 26 articles and 1438 patients with baseline intermediate LVEF (average 43%) found an 84.8% successful implantation rate with improvement in LVEF by 6% [35]. HBP may be

a future pacing modality with improved implantation rates and perhaps less operative risk in this population.

The same concepts are seen in the limited data on post-AV nodal ablation and CHD patients. Often these patients will also have reduced LVEF and other structural abnormalities present, and patients with CCAVB and CHD appear to clinically benefit from CRT. Although there are no RCT data to prove the benefit of CRT or LV pacing over traditional RVP, the limited data of case reports and case series show that there is clinical benefit from ventricular resynchrony particularly in those with a wide QRS and visualized dyssynchrony. In post-AVJA patients, CRT appears to benefit these patients over traditional RVP in terms of preserving LVEF and reducing clinical progression of HF and HF hospitalization. PAVE along with studies by Brignole and Mittal et al. found a drop in LVEF in RVP after AV nodal ablation as compared to biventricular pacing. Clinically, Mittal and colleagues found a relative reduction in heart failure hospitalizations in patients with CRT compared to those with RVP, but baseline LVEF was unavailable. Meanwhile, Brignole and colleagues found a reduction in clinical worsening of HF and HF hospitalizations in patients who received CRT as compared to RVP; although the average LVEF in this study was reduced, 60% of patients had intermediate or preserved EF. It is unclear, therefore, whether CRT after AVJA would benefit all patients universally, irrespective of LVEF, although physiologically maintaining some degree of synchrony (with biventricular pacing or HBP) remains the most attractive option.

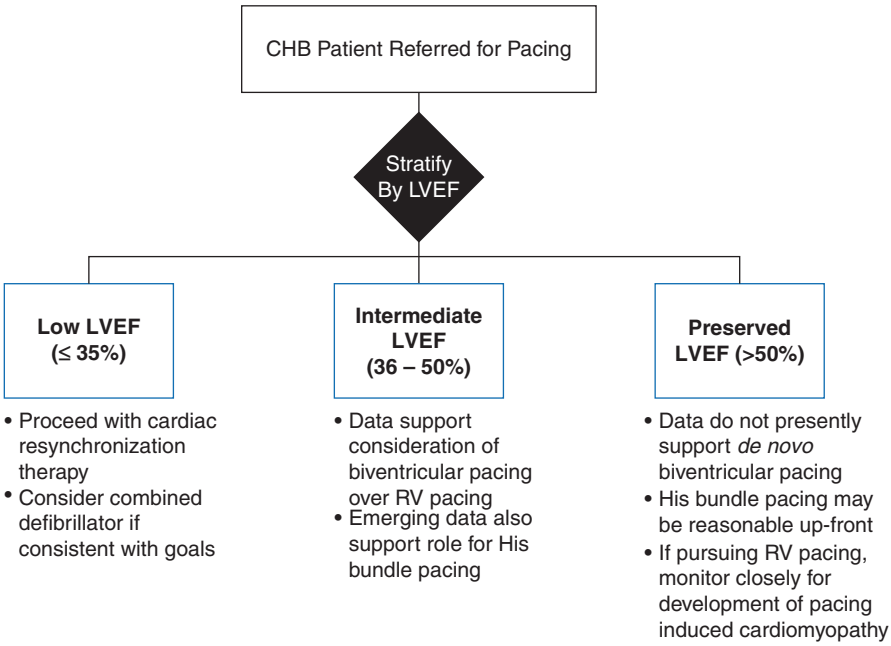

Fig. 5.2 Suggested decision tree for device selection in patients with complete heart block

Conclusion

The weight of the evidence supports the use of CRT in patients with reduced LVEF, is likely beneficial in those with intermediate LVEF, but should not be routinely pursued in patients with preserved LVEF, particularly due to higher perioperative risk and due to the technical difficulty of implanting an LV lead in a minority of patients. A suggested approach is outlined in Fig. 5.2. Future research should focus on better risk stratifying patients at risk for RV pacing-induced cardiomyopathy beyond baseline LVEF, particularly with respect to underlying biomarkers or genetic predisposition to structural or functional decline. In addition, alternative site pacing, including His bundle pacing and conduction system pacing, should also be considered as a complement or alternative to biventricular pacing.

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